**<u>SUPPLEMENTAL MATERIALS FOR:</u> Tetratricopeptide Repeat Domain 7A Mutations Results in a Severe Form of Very Early Onset Inflammatory Bowel Disease.**

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## SUPPLEMENTAL METHODS

**Computational Network Analysis**: To better understand the structure of TTC7A network and the potential causal relationships among genes comprising this network, we constructed a probabilistic causal gene network using an integrative Bayesian network reconstruction algorithm [1,2] by integrating the gene expression from existing networks[3], and experimentally derived pathway information.

**Constructs and Western Blot Methods:** A C-terminal *myc*-tagged TTC7A cDNA was subcloned into the pCMV6 entry vector purchased from Origene (USA). Point mutations at E71K, ~~and~~ Q526X and A832T were created by site-directed mutagenesis using the QuikChange II Kit (Stratagene, USA). Primers for $TTC7A^{WT}$, $TTC7A^{E71K}$, $TTC7A^{Q526X}$ and $TTC7A^{A832T}$ were designed and synthesized by CDI (Canada) according to human TTC7A sequence in NCBI (NM_020458).Primers for $TTC7A^{E71K}$ Forward:5' GAAATTGCTGCTGGCTAAGGCCCTCCTGGAGC3', Reverse: 5'GCTCCAGGAGGGCCTTAGCCAGCAGCAATTTC 3'; Primers for $TTC7A^{Q526X}$ Forward: 5' GAGAGGGCTCAGTAGCTGGCGCCCAG3', Reverse: 5' CTGGGCGCCAGCTACTGAGCCCTCTC 3'; Primers for $TTC7A^{A832T}$ Forward: 5'CCAGGGCCAGAACGAGGCTACTTGACTG3', Reverse: 5'CAGTCAACGGTAGCCTCGTTCTGGCCCTGG 3'. Sanger sequencing on an ABI 3730 DNA analyzer (Life Technologies) was used to confirm sequences. Henle-407 and HEK29T cells were transiently transfected according to standard protocols with equal amounts of DNA. Over-expression of TTC7A was evaluated by Western blotting with both Myc and TTC7A primary antibodies and anti-mouse HRP-conjugated secondary antibodies.

**Knockdown of Endogenous TTC7A by shRNA:** GIPZ human TTC7A shRNA (GFP tagged) targeting coding regions and GFP tagged control shRNA (Thermo Scientific, USA) were transfected into Henle-407 cells with Lipofectamine 2000 (Life Technologies, USA). Twenty-four to 72 hours post-transfection, TTC7A knockdown was evaluated by Western blot and real-time PCR. To establish cell lines stably expressing the TTC7A shRNA, transiently transfected cells were sub-cultured and placed on selection media with puromycin (1μg/ml, Life Technologies). Twenty-four hours post transfection, the stable Henle-407 control and TTC7A knockdown cell lines were maintained on DMEM supplemented with glutamine, 10% FBS, and 0.5μg/ml puromycin.

**Western Blotting:** Western blotting was carried out by standard protocols. Briefly, membranes were incubated with the following primary antibodies: anti-TTC7A (Proteintech, USA), anti-myc, anti-GAPDH, anti-α-tubulin (Sigma-Aldrich, USA), anti-caspase3 (Cell Signaling Technology,USA), anti-GFP (MEDIMABS, Canada), and anti-PI4KIIIα (Pierce Biotechnology, USA). HRP-conjugated anti-mouse and anti-rabbit secondary antibodies were incubated with the membrane followed by West-ZolPlus Western Detection Reagent (FroggaBio, Canada). Chemiluminescence was visualized using the FluorChem E imaging system (ProteinSimple, Santa Clara, CA, USA).

**Cell culture:** Henle-407 human intestinal-like and Caco-2 intestinal epithelial cells from ATCC were cultured in Dulbecco's Minimum Essential Medium (DMEM) supplemented with glutamine, 10% fetal bovine serum (FBS), penicillin and streptomycin (100IU/ml). Cell viability was determined by counting the number of viable cells with the Trypan blue dye exclusion test.

**Histology:** For Patient 1 biopsies of duodenum and colon were fixed in 10% buffered formalin, embedded in paraffin and sections staeined with heamatoxilin and eosin using routine methods. For EM, biopsies were fixed in 2% gluraldehyde in phosphate buffer, post fixed in 1% osmium tetroxide and embedded in Epon**.** Paraffin-embedded human appendix tissue sections were subjected to heat-mediated antigen retrieval by boiling in Dako target retrieval solution, PH9 (Dako) for 35 minutes. Tissue sections were then washed and subjected to blocking of non-specific binding and endogenous peroxidase activity using a solution containing 10% donkey serum, 1% hydrogen peroxide and 0.05% sodium azide (2 x 15 minutes). TTC7A was labeled using a rabbit anti-human TTC7A antibody (C-terminus) (Abgent, AP16342b) followed by a peroxidase-conjugated anti-rabbit secondary antibody (711-035-152, Stratech Scientific Ltd). Signal amplification was performed using a cyanine tyramide reagent (Perkin Elmer). Signal amplification was performed using a Cy3 tyramide reagent (Perkin Elmer). Sections were finally dried and mounted in mounting media containing DAPI (Vectashield) then viewed under a fluorescence microscope.

**TTC7A Co-Immunoprecipitation and Trypsin Digestion:** HEK293T cells were transiently transfected with FLAG-epitope tagged human wildtype, E71K and Q526X TTC7A. Cells were lysed two days post transfection and TTC7A was immunoprecipitated using M2 Anti-FLAG-agarose (Sigma) for 2 hr at 4°C. The bound proteins were washed twice with lysis buffer (150mM NaCl, 50mM HEPES, 1% Triton X-100, 10% glycerol, 1.5mM MgCl2, 1.0mM EGTA), twice with low-salt HNTG (150mM NaCl, 20mM HEPES, 0.1% Triton X-100, 10% glycerol), and once with HPLC-grade water. Bounded proteins were eluted off the FLAG-agarose with sequential washes of 0.15% trifluoroacetic acid (TFA). Proteins were reduced using 45mM DTT and cysteine residues were blocked with 100 mM iodoacetamide. Trypsin digestion was performed overnight at RT. The peptide solution was purified through a C18 resin Spin Column (Thermo-Scientific) with bound proteins eluted using 0.1% trifluoroacetic acid (TFA)/40% acetonitrile.

**Immunoprecipitation:** HEK 293T cells (overnight split ~ 5,000,000 cells) were transfected with Myc-tagged wild type and mutated TTC7A (E71K, Q526X, and A832T) constructs using lipofactamine 2000 according to instructions, 24 hours after transfection. Lysates were collected after centrifugation at 10,000g for 20min at 4°C. The supernatant (~1mg) was incubated with 1mg of antibody plus 10 ml of protein G bead at 4°C for 3hours. Bead plus precipitate were recovered by centrifugation. Western blotting with anti-MYc and PI4KIIIα antibody was carried (Thermo Scientific, USA).

**Tandem Mass Spectrometry:** Peptide mixtures were separated on an automated nanoliter-scale liquid chromatography (LC) system (Easy-nLC, Proxeon Biosystems A/S, Odense, Denmark) then detected using a Thermo-Fisher linear ion trap mass spectrometer system (LTQ, Thermo, San Jose, CA). An in-depth protocol describing all MS settings is described[5].

**MS/MS Data Analysis:** Tandem mass spectra data obtained were extracted using BioWorks (Thermo Scientific, Waltham, MA). To determine the identity of the peptide fragments, MS/MS samples were analyzed using SEQUEST (Thermo Finnigan, version 27) set to search the Swiss-Prot database assuming trypsin digestion. Scaffold (version Scaffold-01.06.05, Proteome Software Inc., Portland, OR) was used to confirm and validate MS/MS-based peptide and protein identifications. Probability thresholds for peptide and proteins identification were set at ≥95% and ≥90%, respectively, as determined through the ProteinProphet™ algorithm[6]. To determine if the quantity of PI4KA immunoprecipitated by E71K was different than the wildtype, the area under selected peptide peaks from the TTC7A MS1 spectrum was evaluated between the two genotypes and normalized across biological replicates. This area represents the relative abundance of each peptide.

## CASE HISTORIES

**Family-1:** The patient was a female born at 36 weeks of gestation with a weight of 2.461 kg (3rd percentile) after a normal pregnancy via spontaneous vaginal delivery. The mother was Caucasian with 3 healthy children from a previous marriage (ages 17, 12 and 9), and the father was from Sudan with no children but with 7 healthy siblings. Both were noted to be healthy. Watery and bloody diarrhea started almost immediately after birth, along with early feeding intolerance and emesis. On day of life #9, she was admitted to hospital for possible cow's milk protein allergy and failure to thrive. Various formulas were attempted including elemental formulas, with no effect on the diarrhea. While in hospital the diarrhea was classified as secretory with stool volume more than 100 ml/kg/day, high sodium content and no reduction in the amount of stool during fasting. Physical examination was unremarkable apart of mild frontal bossing. Skin examination was normal. The patient required total parental nutrition due to high stool output and intolerance of feeding. On blood work, she was found to have a profound hypoalbuminemia and mild peripheral eosinophilia (0.6-0.9). Her stool was found to have polymorphoneutrophils.

In the first 3 months of her life, the patient developed recurrent fevers. Some without a clear etiology and most due to recurrent bacteremia with Streptococcus viridans, Coagulase Negative Staphylococcus, as well as multiresistant Serratia in both urine and blood. Subsequent renal workup was negative for any anatomical abnormalities.

An initial workup for immunodeficiency's found a low total immunoglobulin level as well as a low lymphocyte count (0.6-1.6) with a normal absolute neutrophil count (2.8-16). CD4, CD8, CD19 and CD3 counts were all within normal limits. Neutrophil function, tested via Neutrophil oxidative burst index (NOBI) was found to be normal.

At 4 months of age, steroids were administered after findings suggestive of colitis on imaging. The patient had an initial mild response with a reduction in the blood content of stools and improved serum albumin level. The treatment was discontinued due to a septic episode.

Endoscopy was performed for the first time at 5 months of age and revealed a normal stomach with an edematous and friable duodenum. Colonoscopy showed an edematous colon with patchy pancolitis, more pronounced on the left side of the colon. The terminal ileum was not intubated. On pathology, the duodenum was noted to have mild inflammation with an intact epithelium and partial villous atrophy. In the colon, marked mucosal injury with regenerative changes and extensive apoptosis involving the crypts and surface epithelium were noted. The lamina propria lacked chronic inflammatory cells with scattered eospinophils and neutrophils. Viral staining was negative. No signs were found in support of tufting enteropathy or microvillous inclusion disease (MVID), as there was a normal villous brush border in the intestine on electron microscopy.

The patient was then transferred to our institution at 6 months of age for further workup for possible immunological defect and intestinal rehabilitation. Mild eosinophilia up to $2X10^9$/L and hypoalbuminemia (13 g/L) were noted again.

On further immunological testing, she was noted to have persistently low immunoglobulin's, specifically with a decreased IgG1 (1.06 g/L) and IgG3 (0.09 g/L) subclass and low lymphocyte count (Range 0-2.56 x 10^9 cells/L). Testing for HIV was negative by PCR. Telomere length was found to be normal. Thymic biopsy was done which showed a normal architecture with low lymphocytes. Extensive genetic testing was done which showed no defects in IL10R-alpha, IL10R-beta, IL10, CD3E, CD3delta, CD25, STAT1, RAC2, IL7R, SLCA7 and RMRP (Carried out in the Laboratory of Dr. Chaim Roifman). Microarray analysis, karyotype, and chromosome breakage studies were reported as normal as well.

At 9 months of age, a second endoscopy was performed, which showed an edematous and friable duodenum with a grossly normal stomach. Colonoscopy was limited due to the severity of the inflammation, but showed severe colitis up to the mid-transverse colon with severe friability and exfoliative mucosal changes and sloughed mucosa within the colonic lumen. Pathology showed on all biopsies severe villous atrophy, gland dropout and severe crypt apoptosis with exploding crypts reminiscent of acute gastrointestinal graft-versus host disease (GVHD). The lamina propria was noted to have some lymphocytic infiltration, occasional plasma cells, eosinophils and scattered neutrophils. The severity of the epithelial injury, along with the regeneration, was strikingly reminiscent of acute GVHD and intestine allograft rejection.

IVIG was used on 4 occasions due to the suspected immunedeficiency with low immunoglobulins and history of repeated infections with no clear improvement. Octreotide was used with some decrease in stool output.

After the second endoscopy, the patient was started on methylprednisone at a dose of 2 mg/kg. There was some initial subjective response, (decrease in the amount of blood seen in the stools), but this was not sustained.

At 11 months of age, she developed an increased work of breathing and was found to have parainfluenza A which led to severe ARDS and death due to respiratory failure after her first birthday.

**Family-2**: The first child was born to non-consanguineous parents at 35wks gestation. There was polyhydramnios and the mother was hospitalized for preterm labor prior to delivery. Shortly after birth the patient was admitted for suspicion of duodenal stenosis.

At admission the blood work was as following: leukocytes 14000/µl; hemoglobin 19.0 g / dL; CRP 16 mg / L; creatinine 1.1 mg / dL; Bili Total 8.3 mg / dL; indirect Bili 6.5 mg / dl; INR 1.36; PTT 52 sec. Electrolytes were in the normal range. Screening for inherited metabolic diseases and TORCH infections was negative.

At admission there was suspicion of a duodenal stenosis and an abdominal ultrasonography on showed a horseshoe-shaped liquid-containing structure in the configuration of a duodenal C until duodenojejunal junction in the left upper abdomen. There were otherwise no further dilated bowel loops and no more liquid in the region of the middle and lower abdomen. Therefore a transverse upper abdominal laparotomy was preformed and showed a short segment of proximal jejunal atresia with perforation. The segment was resected and end-to-end was anastomosed. The rest of the small bowel and colon was normal. Shortly after, the patient deteriorated and re-laparotomy was conducted and identified new sections of atretic bowel that were resected. Due to the pronounced short bowel syndrome, the patient was placed on long-term parenteral nutrition. The patient continued to have FTT and elevated inflammatory markers with partial septa weeks showing no evidence of infection. The Patient remained unstable and was transferred to the ICU where he died due to suspected pulmonary embolism

The second child was admitted shortly after birth with jaundiced - grayish skin color, distended abdomen, sparse peristalsis and low blood pressure.

Labs at admission were: Lc 12240/µl, Hb 11.6 g / dl, Tc 168.000/µl, CRP 61 mg / l; GOT 879 U / l , GPT 596 U / L , GGT 123 U / L.

On admission, contrast imaging of the small bowel demonstrated several small atresia of small bowel. Surgery was performed and found jejunal atresia that were resected. Shortly after resection the disease progressed rapidly and the patient passed away before 19 months of age.

**Family-3:** A 5-month old female infant was referred for investigation of failure to thrive (FTT). Her parents were consanguineous. She had history of bloody diarrhea that had begun shortly after birth and would occur up to 12 times per day, but in low volumes.

Physical examination revealed that all growth parameters were below the fifth percentile of growth chart. Her weight was 2.8 kg at the birth and 4.3 kg at the fifth month. Also, at presentation, her height and head circumference were 60 and 39 cm, respectively. She had oral and diaper candidiasis. There was neither hepatomegaly nor splenomegaly.

Stool analysis showed PH=8, WBC=10-12, RBC=0-1 and it was negative for fat droplets. Complete blood cell count (CBC) demonstrated WBC=14700 (PMN=37%, lymph=54%, Eos=0.4%), Hb=9.7 and Plt=540000. ESR was 39. Serum immunoglobulin assays revealed IgG=251 mg/dl, IgM=70 mg/dl, IgA=72 mg/dl, IgE=50. NBT was 100%. Lymphocyte markers showed CD3=71%, CD4=54.6%, CD8=20.8%, CD16-56=3.4%, CD19=17.2%. ASCA was 2.3 (negative). Anti tetanus Ab was 0.5 and anti diphtheria Ab was 0.4. Pseudomonas was grown in the blood culture.

Endoscopic investigation was performed with macroscopic finding of normal esophageal mucosa, but erythematous stomach's body and antral mucosa. Microscopic finding was moderate infiltration of lymphoplasma cells in lamina propria of antrum and duodenum (D2).

Macroscopic findings in colonoscopy included mainly loss of vascularity pattern and edema of the mucosa. Also, there was nodularity in rectal mucosa. Microscopic examination showed variable sized glandular structures with regenerative changes, but all of them had preserved goblet cells. Lamina propria contained excess number of inflammatory cells composed of eosinophils and few PMNs. Many apoptic cells and marked capillary dilation was noted. No granuloma and crypt abscess was seen.

She received antibiotics, partial parenteral nutrition and hypoallergenic diet. She was discharged with partial recovery, but returned with similar condition (FTT and diarrhea) in 14 months of age. She had colitis again. Management of her condition was similar to previous and partial remission was achieved.

Her sister which was a 2-month old infant also presented with diarrhea and diminished weight gain. She was the result of preterm delivery with birth weight of 2 kg and failed to gain weight subsequently. Similar to her older sister, she also had diarrhea, which had started shortly after birth.

All growth parameters were below the fifth percentile of growth chart. She had mild periorbital and extremities edema.

Stool examination showed: WBC=30-40, RBC=15-20, mucus was 1+, occult blood was 2+ and it was negative for fat droplets.

Results of laboratory tests included WBC=14800 (PMN=27% and lymph=62%), Hb=9.9 and Plt=469000 in blood cell count. ALT=69, AST=88, Alb=1.8 and total protein=3.2.

Treatment initiated with suspected diagnosis of allergic colitis and she was discharged with partial improvement. However, 2 months later, she returned with similar complaint despite adequate hypoallergenic diet. She had history of gross blood in the stool.

Laboratory examination in this admission showed WBC=25800 (PMN=32.3%, lymph=48% and Eos=1.6%), Hb=8.6 and Plt=360000 in blood cell count.

Serum immunoglobulins demonstrated IgG=228 mg/dl, IgM=51 mg/dl, IgA=28 mg/dl, and IgE=18. NBT was 100%. Lymphocyte markers were as follows: CD3=90.55%, CD4=49.33%, CD8=44.93%, CD16-56=3.36% and CD19=1.48%. Anti tetanus and anti diphteria Ab were 0.09 and <1, respectively. VDRL was negative. CMV IgG=2.6 and CMV IgM=0.6. Neither of the tests proposed a definite diagnosis for her and again she discharged after partial recovery.

She had another admission at $9^{th}$ month from birth. In this admission, her body weight was 3.3 kg and there was peripheral edema. β-hemolytic streptococcus group A was cultured from throat.

Colonoscopy was performed and macroscopic examination showed loss of vascularity pattern and edema of mucosa with sloughing. Microscopic findings included fibrotic changes in fragments of intestinal wall, presence of distorted architecture in a few colonic glands, paneth cell metaplasia and focal goblet cell depletion. Surface epithelium was detached in most areas with focal acute and chronic inflammatory cell infiltration in which eosinophils were as 10-12/hpf.

She received prednisolone in this admission, because infantile Crohn's disease was suspected.

Finaly, she was admitted with severe watery diarrhea (>18 times per day), fever, cough and respiratory distress at 11$^{th}$ month of age. Blood cells count reported: WBC=31900 (PMN=55%, lymph=34%, Eos=0.3% and Mono=9%), Hb=8.7 and Plt=656000; CRP=44. Candida grew in blood cultures. Chest X-ray showed bilateral consolidation in lungs with air bronchogram in lungs apex. Colonoscopy was repeated with similar results to previous one. Colon biopsy for CMV PCR was positive. She received wide-spectrum antibiotics, amphotricin B and gancyclovir, but unfortunately she did not respond and expired.

**SUPPLEMENTAL FIGURES**

## Supplemental Figure 1:

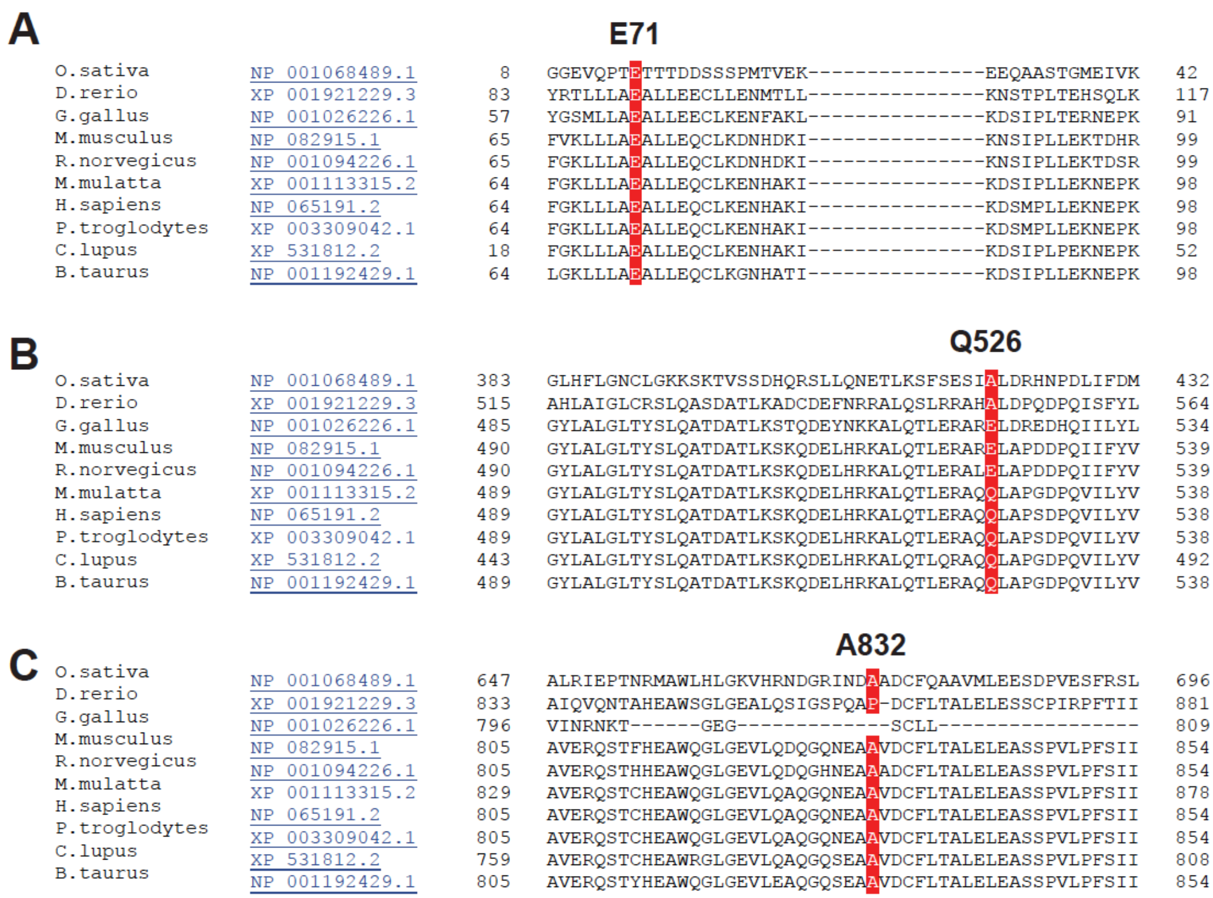


**Figure 1. Species homology alignments at sites E71, Q526, and A832 in TTC7A reveal strong amino acid conservation.**
Full-length human TTC7A was selected from HomoloGene from NCBI, and a multiple protein sequence alignment was generated using MUSCLE.

# Supplemental Figure 2:

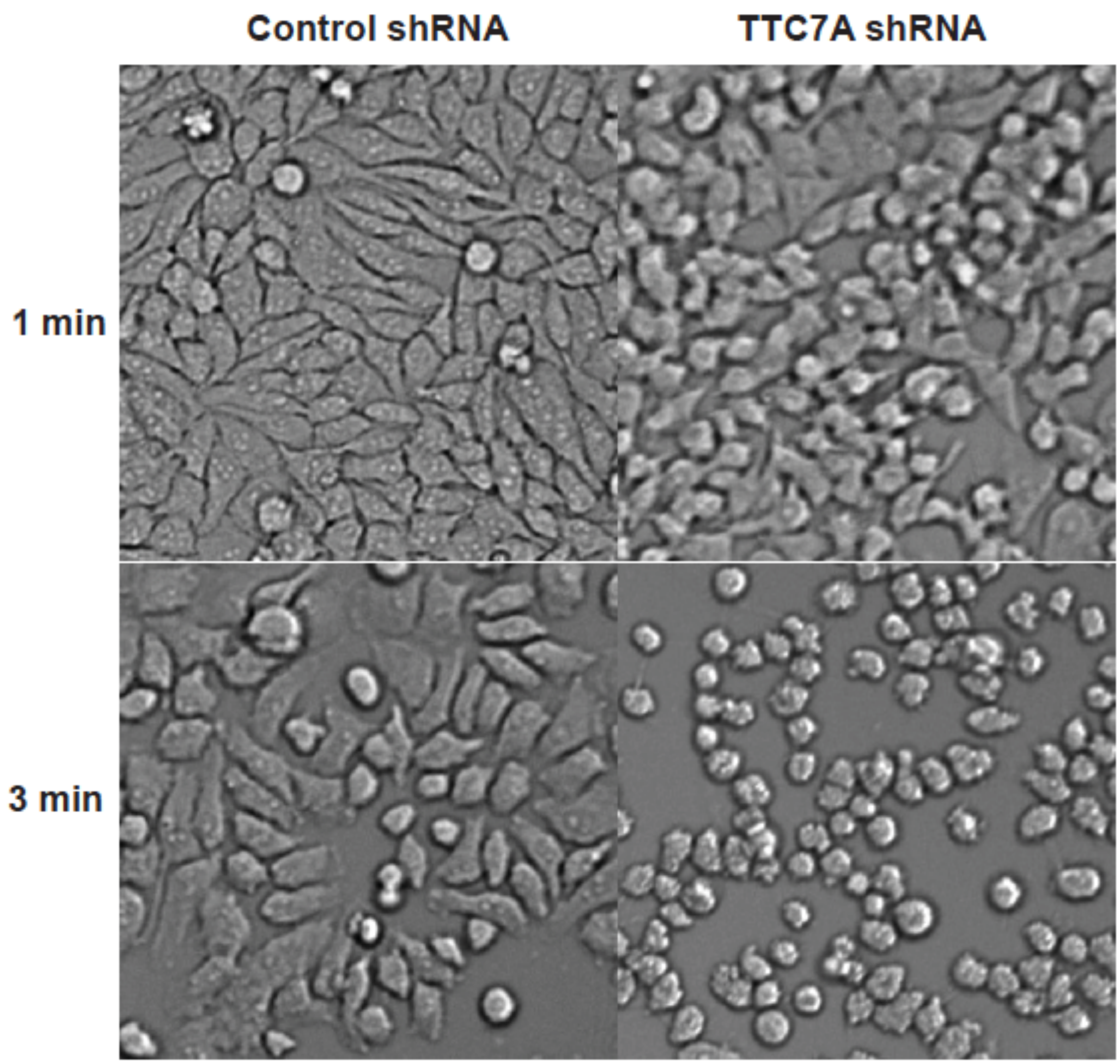


**Figure 2. Cellular Adhesion in TTC7A-Knockdown.**
Given the importance of cellular adhesion in epithelial cell function, we evaluated the adhesion of TTC7A-Knockdown and control Henle-407 cells after treatment with trypsin-EDTA. The total dissociation time, defined as the time required for complete dissociation of all cells from the tissue culture plate, of the TTC7A-Knockdown Henle-407 cells was significantly lower than that of the control Henle-407 cells.

Supplemental Figure 3:

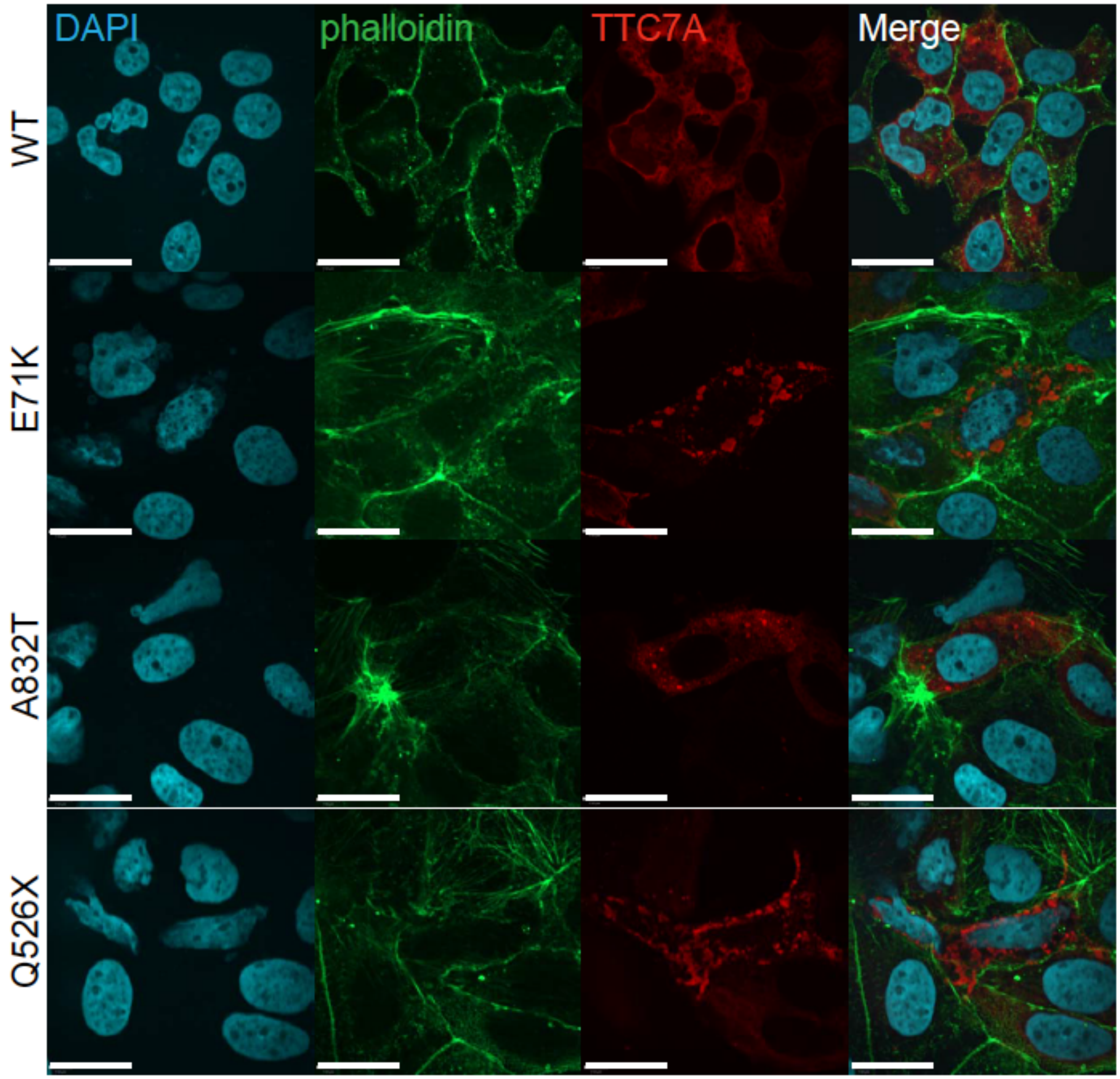


**Figure 3: Expression of TTC7A mutants in Caco-2 cells leads to morphological changes.** Caco-2 cells were transiently transfected with Myc-tagged wild-type and mutant (E71K, Q526X, and A832T) TTC7A and immunostained using anti-Myc antibody and Alexa Fluor-488 phalloidin, to visualize actin morphology. Transfection with WT-TTC7A demonstrated diffuse cytoplasmic distribution of TTC7A and distinct cell-to-cell borders with distinct cortical actin staining. Overexpression of E71K, A832T, and Q526X TTC7A demonstrated cytoplasmic accumulations of Myc-TTC7A in addition to disrupted cortical actin staining suggestive of adhesion defects or loss of cellular polarity. All panels are stained with DAPI to visualize cell nuclei. Scale bars = 25 µm.

## Supplemental Figure 4:

**A**

| | |
|---|---|
| PI4KA | UBR5 |
| MDN1 | HUWE1 |
| NUP205 | HECTD1 |
| LMB1 | VCP |
| PSMD1 | FANCA |
| DNAJC7 | COPG2 |
| USP9X | NUP188 |

**B**

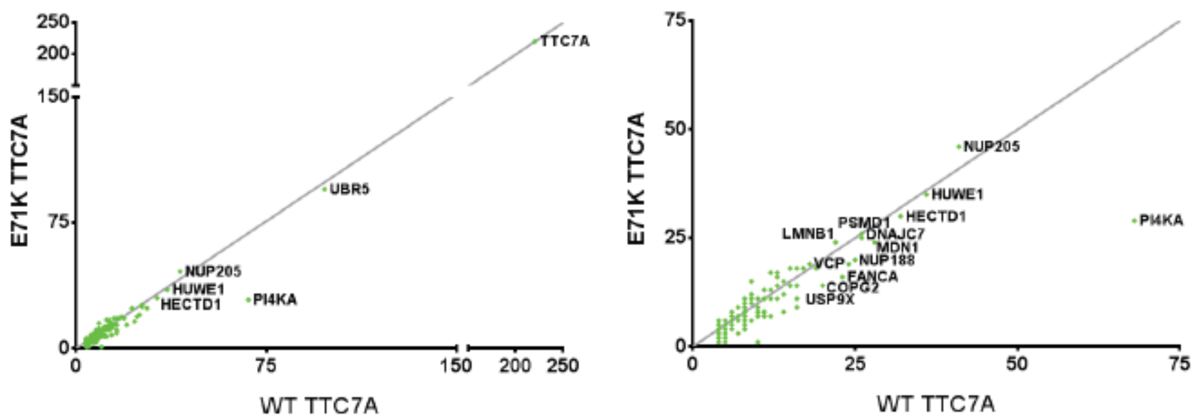


**Figure 4. Tandem mass spectrometry identifies 14 putative TTC7A interacting proteins which co-immunoprecipitate with overexpressed TTC7A.**

A. FLAG-tagged WT or E71K TTC7A was overexpressed in HEK293T cells. Cell lysates were immunoprecipitated using FLAG-agarose. Bound proteins were trypsin digested then eluted, and run on a tandem mass spectrometry. Putative interactors were prioritized based on the number of spectral counts present in the sample compared to the spectral counts in the negative control. B. Total spectral counts for proteins immunprecipitated with WT (x-axis) and E71K (y-axis) TTC7A were plotted as an x-y scatter plot. Each point represents a protein present in both samples. Both panels represent the same data on difference scales. A line representing y=x was plotted for reference. High fidelity hits will contain greater numbers of spectral counts, while differential binding to E71K versus WT can be indicated by deviations from y=x.

## Supplemental Figure 5:

A

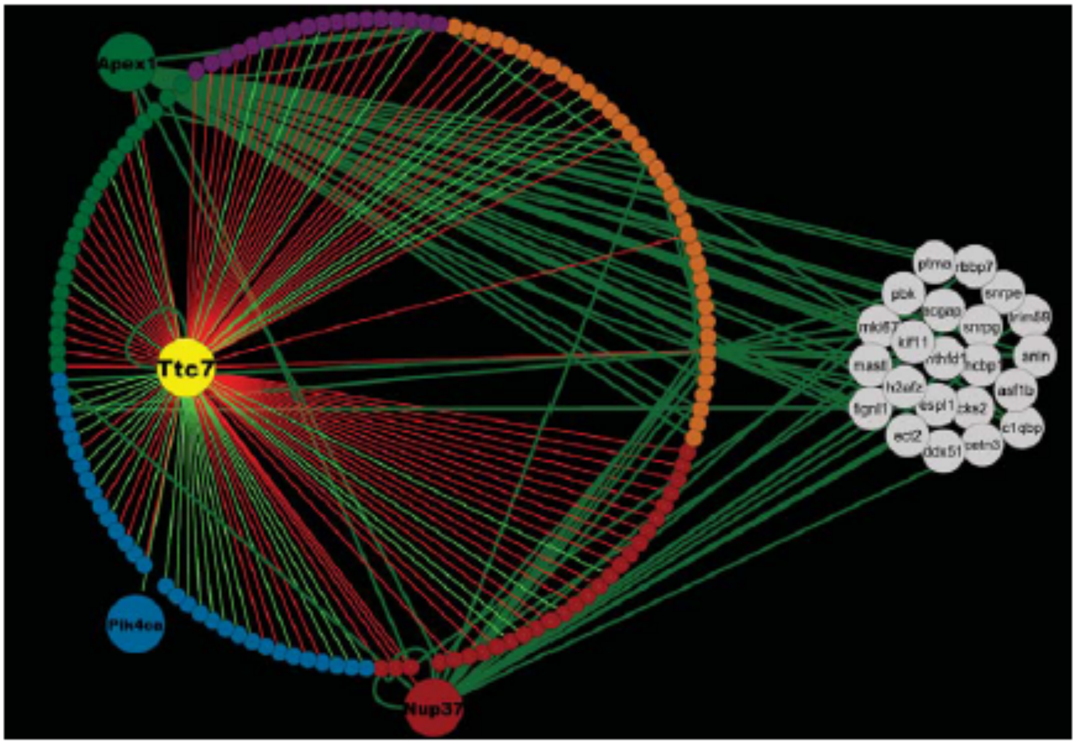


**Figure 5. TTC7A Network Analysis.**

Subcomponent of the Ttc7 subnetwork (Supplementary Table 2) connected to different pathways including viral transcription (5.7-fold enriched; Fisher Exact, FET, P = 1.6e-18), viral infection (5.4-fold enriched; FET P = 1.8e-18), translational elongation and termination (5.8-fold and 5.7-fold enriched, FET P = 5.5e-22 and 1.9e-19, respectively), and mitotic cell cycle (3.5-fold enriched; FET P = 4.0e-25). Green edges indicate positive correlations and red edges indicate negative correlations. The heavier green edges reflect stronger correlations (correlation coefficient > 0.9) among genes (light grey nodes) associated with the genes in the Ttc7 subnetwork that are correlated with Ttc7 small bowel expression. The edge between Ttc7 and Pik4ca is directed, with Ttc7 supported as causal for Pik4ca in the mouse cross small bowel expression data.

| SNP | Base Position | Position in EFR3B | Minor Allelic Frequency | CD GWAS P-Value | CD IChip P-Value | CD Meta-Analysis P-Value | OR | L95-U95 |
|---|---|---|---|---|---|---|---|---|
| rs11125884 | 25092768 | 5' Upstream | 0.48 | $2.39x10^{-4}$ | $2.18x10^{-11}$ | $3.15x10^{-14}$ | 1.12 | 1.08-1.15 |
| rs12466350 | 25093473 | 5' Upstream | 0.48 | $2.07x10^{-4}$ | $2.18x10^{-11}$ | $2.88x10^{-14}$ | 1.11 | 1.09-1.15 |
| rs1077492 | 25139939 | Intron 1 | 0.48 | $1.50x10^{-4}$ | $2.18x10^{-11}$ | $1.90x10^{-14}$ | 1.11 | 1.09-1.15 |
| rs17801121 | 25157791 | Intron 1 | 0.29 | $7.04x10^{-4}$ | $1.64x10^{-2}$ | $3.631x10^{-4}$ | 1.05 | 1.01-1.09 |
| rs7575363 | 25196418 | Intron 4 | 0.30 | $6.43x10^{-3}$ | $1.64x10^{-2}$ | $3.41x10^{-4}$ | 1.05 | 1.00-1.09 |
| rs3731631 | 25212926 | Exon 14 | 0.29 | $1.53x10^{-3}$ | $1.64x10^{-2}$ | $1.13x10^{-4}$ | 1.05 | 1.01-1.09 |

**Supplemental Table 5: Genetic Association of EFR3B SNPs and CD from the IIBDGC**

GWAS, Immunochip, and meta-analysis database from the International IBD Genetics Consortium (IIBDGC; (http://www.ibdgenetics.org[7])

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